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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/998,195
Filing Date: December 03, 2001
Appellant(s): SENANAYAKE ET AL.

Mark Kafka (for Anthony M. Insogna)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/13/09 appealing from the Office action mailed 3/20/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,047,432 Housley 09-1991

Jeffery, J. E. "Synthesis of sibutramine, a novel cyclobutylalkylamine useful in the treatment

of obesity, and its major human metabolites", J. Chem. Soc. Perkin Trans. I, 1996, pp 2583-2588.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 2-6 and 74-78 rejected under 35 U.S.C. 103(a) as being unpatentable over combined teachings of Jeffery et al and Housley et al.

Instant claims are directed to hydroxylated derivative of sibutramine, which are stereoisomers. Claims 2 and 74 are directed to stereomerically pure derivative and composition, when R1 and R2 are both hydrogen.

Jeffery et al teaches stereoisomers of hydroxylated derivative of sibutramine, similar to claimed herein. See for example, compound 5a, on page 2583, last compound in column 1, on page 2587, and last compound in column 1, on page 2588, wherein it is expressly teaching the stereoisomers of the derivatives. The difference between the reference and herein claimed compounds and composition is that the reference has not made every derivative that is claimed. The difference between the reference and herein claimed compounds is that the reference is not teaching diastereoisomeric compounds and multiple chiral centers.

Housley et al is teaching that structurally similar compounds as claimed herein can exist in different optically active form, when the compounds contain one chiral center, the compounds can exist in two enentiomeric forms. When the compounds contain more than one chiral center, the compounds can exist in diastereoisomeric forms, similar to claimed herein. Even geometric isomeric compounds have been taught. See column 5, lines 48-60. Also see column 7, lines48-49.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify Jeffery et al by including the diastereoisomers and multiple chiral centers in the compound, as taught by Housley et al, because the latter reference is expressly teaching that the diastereoisomers and chiral centers are old in the structurally similar compounds.

(10) Response to Argument

Appellants allege that a prima facie obvious case has not been established by the examiner. They further cite KSR for the obviousness determination. Appellants urge that Jeffery does not disclose compounds encompassed by claim 2 or 4. Appellants urge that the reference teach cis and trans isomers as against stereoisomers claimed in herein. At the same time, appellants admit that the reference expressly teaches a mixture of diastereoisomers, and that no attempt was made to isolate them. Appellants further allege that the Examiner has not provided any reason as to why one of ordinary skill in the art would have prompted to isolate compounds as claimed in herein. Appellants further point out that Housley does not cure the deficiency of Jefferey. Appellants have cited Ex parte Holy in reply to the Examiner's citation of In re Adamson. The appellants point out that allegations of structural similarity alone are an improper basis for the rejection. Finally, appellants argue that even assuming, arguendo, a prima facie case were established, Jefferey rebuts such a prima facie case because it teaches away from the instant claims. Since Jefferey discloses that the two demethylated metabolites of sibutramine are predominantly responsible for the activity of sibutramine, those skilled in the art would have considered these metabolites to be better alternatives to the claimed hydroxylated metabolites.

The examiner respectfully disagrees with the appellants' Arguments with respect to the obviousness determination. While it is true that the Jefferey reference is directed to the mainly cis/trans isomerism, however, a fact that Jefferey compound structures do have stereocenters, and taken together with the Housley reference, one of ordinary skill

in the art would be motivated to isolate the stereo compounds. With respect to Ex parte Holy, it is first noted that the Holy decision is **unpublished**. Furthermore, because in Jeffery et al, the teachings are not specific to the racemic compounds. There is enough suggestion to arrive at the stereocenters, specifically in view of the chiral carbon atom.

It has been held in Aventis Pharma Deutschland GmbH v. Lupin Ltd. That "Teaching, suggestion, or motivation" test for obviousness of claimed invention should not be applied as rigid and mandatory formula, since it is necessary to show some articulated reasoning, with some rational underpinning, to support legal conclusion of obviousness, but such reasoning need not seek out precise teachings directed to specific subject matter of challenged claim; in present case, finding that invention of patent claiming purified form of ramipril used in treating high blood pressure would have been obvious does not require explicit teaching to purify ramipril from prior art mixture in which it is active ingredient.

Claimed "5(S)" stereoisomer of ramipril in form substantially free of other isomers, used in treatment of high blood pressure, would have been obvious over cited prior art references, since, in chemical arts, structural similarity between claimed and prior art subject matter creates prima facie case of obviousness if prior art gives reason or motivation to make claimed composition, since claimed ramipril in present case is purified form of mixture that existed in prior art, since it is ordinarily expected that concentrated or purified ingredient will retain same properties it exhibited in mixture, and that those properties will be amplified when ingredient is concentrated or purified, since prior art provides sufficient reason to look to 5(S) configuration as therapeutically active

ingredient in prior art mixture, since prior art patent specifically taught that stereoisomers of ramipril could be separated by conventional chromatographic or fractional crystallization methods, and there is no evidence that isolating 5(S) stereoisomer was outside capability of skilled artisan, and since patentee plaintiffs failed to rebut this prima facie case by showing that 5(S) ramipril exhibited unexpected results over prior art mixture.

In the chemical art, it has been long held that "structurally similarity between the claimed and prior art subject matter proved by combining references, where the prior art gives reason or motivation to make the claimed product, creates a prima facie case of obviousness." Takeda Chem. Indus, Ltd. V Alphapharm Pty., Ltd., (Fed. Cir. June 28, 2007) (quoting In re Dillon, 919 F.2d 688, 692[16 USPQ2d 1897] (Fed. Cir. 1990) (en banc); see also In re Papesch, 315 F.2d 381 [137 USPQ 43] (C.C.P.A. 1963). The "reason or motivation need not be an explicit teaching that the claimed compounds will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a "sufficiently close relationship… to create an expectation," in light of totality of the prior art, that the new compound will have "similar properties" to the old. Dillon, 919 F.2d at 692; see also In re Wilder, 563 F.2d 457, 460 [195 USPQ 426] (C.C.P.A 1977).

In re Adamson is a valid citation in the instant prosecution, as appellants have failed to show any unexpected results. Also see In re Mertz, 97 F.2d 599, 601 [38 USPQ 143] (C.C.P.A. 1938) (holding than an applicant is not entitled to a patent on [an] article which after being produced has a greater degree of purity than the product produced by former methods" unless the purification results in "properties and

characteristics which were different in kind from those of the known product rather than in degree").

Ordinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compound is a mainstay of the chemist's art. If it is known how to perform such an isolation, doing so " is likely the product not of innovation but of ordinary skill in the common sense." KSR, 127 S. Ct. at 1742.

Appellants' last point that Jefferey et al teaches away from the instant claims since it discloses that the two demethylated metabolites of sibutramine are predominantly responsible for the activity of sibutramine, those skilled in the art would have considered these metabolites to be better alternatives to the claimed hydroxylated metabolites, is not understood. The reference expressly teaches hydroxylated derivatives, and as explains supra, the stereoisomers are prima facie obvious as a whole, absent evidence to the contrary. Furthermore, Appellant's assertion of a teaching away is wholly based on two sentences in Jeffery which read in full, "Sibutramine undergoes rapid and extensive metabolism in humans, initially resulting in the demethylated amines 2 and 3. *In vivo* the pharmacological activity of sibutramine is mediated predominantly by these two metabolites." (Page 2583, third full paragraph.) Appellant infers from this that the biological activity of the hydroxylated amine metabolites that render obvious the claimed compounds must be inferior to the demethylated amines. However, the sentences upon which Appellant relies provide no

basis for a conclusion as to the relative biological activity of the demethylated amine metabolites and the hydroxylated amine metabolites. Jeffery states that sibutramine is rapidly and extensively metabolized to the demethylated amines. Therefore, one of skill in the art would expect that they are the predominant metabolites and the reason that the pharmacological activity of sibutramine is mediated predominantly by these two metabolites is that they are present at the highest concentration. Therefore, the statement cannot be viewed as a teaching away from the hydroxylated amine metabolites, particularly in view of the fact that Jeffery goes to great pains to synthesize those very compounds.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SHAILENDRA - KUMAR/

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Supervisory Patent Examiner, Art Unit 1621

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